significant distortions along the three orthogonal axes defined by the three pairs of metal centers. It is, however, clear that the high-frequency modes at 1470 and 1570 cm⁻¹ have been shifted to lower frequency by 30 cm⁻¹ as opposed to less than 10 cm⁻¹ for the monosubstituted systems. This is consistent with the increased π backbonding brought on by the six metal centers.

In conclusion, the Raman spectra of organometallic complexes involving C_{60} provide a clear probe into the symmetry reduction upon reaction of the C_{60} molecular system. This reduction in symmetry results in the observation of both "silent" modes and the splitting of degenerate modes in the Raman spectrum. As the degree of substitution is increased, the perturbations of the C_{60} vibrational modes become stronger and the correlations with the original vibrational spectrum of the parent become less clear. The spectra reported here should be useful benchmarks in characterizing structurally related C_{60} derivatives.

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Communications to the Editor

Synthesis and Conformational Analysis of GM₃ Lactam, a Hydrolytically Stable Analogue of GM₃ Ganglioside Lactone

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Gangliosides have been found to occur in conjunction with the corresponding lactones (e.g., 1) in brain tissue¹ and in the membranes of tumor cells.² The lactones are unstable at neutral pH. We now report the synthesis of the stable lactam 3 and derivatives corresponding to the natural GM_3 lactone. The conformations of 1 and 3 are similar, thus making the lactams potential substitutes for ganglioside lactones in biomedical research. The lactams might be natural products yet to be discovered.

The lactone of GM_3 ganglioside (1, "GM₃ lactone") has been suggested to be a tumor-associated antigen on cells of an experimental mouse melanoma.² In a comparative immunization with GM₃ ganglioside and 1, it was shown that the latter was the stronger immunogen, and it was suggested that it could be the real immunogen despite being a minor membrane component.² The reactivity of a monoclonal anti-melanoma antibody (M2590) with various cells and liposomes was shown² to depend in a threshold, all-or-none fashion on the concentration of GM₃ ganglioside in the cell membrane or liposome. The antibody was found to cross-react with 1.

Acidic conditions favor the lactone in the equilibrium GM₃ ganglioside \Rightarrow GM₃ lactone.³ Since GM₃ ganglioside is an acidic glycolipid, it might induce its own lactonization when the concentration is high in a cell membrane or liposome. This can help to explain the threshold effect described above and may have implications for other sialic acid-containing saccharides.

The equilibrium concentration of GM₃ lactone is low at close-to-neutral pH, and it may therefore be a rather inefficient immunogen. In contrast, the corresponding lactam (cf. 3, "GM₃ lactam") is perfectly stable at neutral pH and should be a good lactone substitute, provided that the overall shape of lactone and lactam is similar. We report the synthesis and conformational analysis of the 2-(trimethylsilyl)ethyl4 (TMSEt) glycoside of GM₃ lactam 3 as well as the spacer glycoside 11 and the neoglycoprotein 12.

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The TMSEt 2'-azidodeoxylactoside 4 { $[\alpha]^{22}_{D}$ +19° (c 1, CDCl₃); ¹H NMR δ 4.40, 4.31 (H-1,1')} was synthesized in 37% overall yield by glycosylation of 2-(trimethylsilyl)ethyl 2,3,6tri-O-benzyl-β-D-glucopyranoside⁴ with 3,4,6-tri-O-acetyl-2-azido-2-deoxy- α -D-galactopyranosyl bromide⁵ followed by deacetylation, formation of the 3',4'-acetonide, benzylation of the 6'position, and removal of the acetonide group. Glycosylation of 4 with the N-acetylneuraminic acid derivative 5^6 according to the method of Lönn et al.⁷ gave the trisaccharide derivative 6 in high yield {71%, $[\alpha]^{22}_{D}$ -13° (c 1, CDCl₃); ¹H NMR δ 4.50, 4.40 (H-1',1) together with the β -anomer (4%). The α -configuration of 6 was determined by NMR⁸ spectroscopy ($J_{C1-H3ax} = 6.15 \text{ Hz}$). Nickel boride $(NaBH_4/NiCl_2 \cdot 6H_2O/H_3BO_3)$ reduction of 6, O-deacetylation of the resulting crude amine, treatment with pyridine to effect the lactam ring closure, and hydrogenolysis of the benzyl protecting groups gave 3 {54%, $[\alpha]^{22}_{D}$ -22.3° (c 0.7, MeOH); ¹H NMR δ 4.69, 4.47 (H-1',1), 4.32 (H-4"), 3.23 (H-2), 2.59 (H-3"eq), 2.02 (NHAc), 1.67 (H-3"ax); m/z calcd for $C_{28}H_{51}O_{17}N_2Si (M + H)$ 715.2957, found 715.2958} after chromatographic purification. Compound 3 was acetylated to give 7 {98%, $[\alpha]^{29}_{D}$ -32° (c 0.8, CDCl₃); ¹H NMR δ 4.54, 4.40 (H-1,1')}. The TMSEt glycoside 7 was transformed⁹ into the α -chloro derivative 8 [100%; ¹H NMR δ 6.20 (H-1)]. Glycosylation of 2-bromoethanol with 8 gave the 2-bromoethyl glycoside 9 {54%, α/β 15:85; $[\alpha]^{25}_{D}$ –27° (c 1.2, CDCl₃); ¹H NMR δ 4.78 (H-1')]. Glycoside 9 was treated¹⁰ with methyl 3-mercaptopropionate to give 10 {82%, $[\alpha]^{22}_{D}$ -23° (c 1.1, CDCl₃); ¹H NMR δ 4.63 (H-1'), 3.69 (COOMe)]. Deacetylation of 10 gave the spacer glycoside 11 $\{86\%, [\alpha]^{25}$ –0.1° (*c* 0.5, MeOH); ¹H NMR δ 4.92, 4.69, 4.48 (H-1 α , H-1['], H-1 β)}, which was used for coupling¹⁰ to bovine serum albumin to give the neoglycoprotein 12 (\sim 21 mol of 11 per mol of BSA according to sulfur analysis¹⁰), useful as an antigen for immunization purposes (Scheme I).

A conformational analysis of GM_3 lactone (1), based on NMR data, was reported by Yu et al.¹¹ A highly rigid structure was proposed, where the lactone ring occupies a chairlike conformation. However, we suggest that a boatlike conformation is instead preferred: (i) both the lactones (1 and 2^{12}) and the lactam (3) show a deshielding of H-4" as compared to the open-form GM₃ ganglioside (δ 3.55 for GM₃ ganglioside and 4.12 for 1, both in

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Figure 1. Stereoview of the superimposed low-energy [MM2(91)] boatlike conformers of the methyl glycosides that correspond to 2 and 3.





^a(a) CF₃SO₃Ag/MeSBr/CH₃CN/CH₂Cl₂/molecular sieves (3-Å)/2 h, then iPr₂NH/-78 °C/1 h. (b) NiCl₂·6H₂O/H₃BO₃/NaBH₄/EtOH/0 °C/20 min. (c) MeONa/MeOH/22 °C/12 h. (d) Pyridine/22 °C/12 h. (e) H₂/Pd-C, 10%/1 atm. (f) Ac₂O/pyridine/22 °C/24 h. (g) Cl₂CHOMe/ZnCl₂/CHCl₃/22 °C/12 h. (h) BrCH₂CH₂OH/CF₃SO₃Ag/molecular sieves (4 Å)/CH₂Cl₂/N₂/-28 \rightarrow 22 °C/16 h. (i) HSCH₂CH₂COMe/Cs₂CO₃N₂/DMF/22 °C/2 s. (k) H₂NNH₂/EtOH/22 °C/12 h freeze drying. (l) *t*-BuO-NO/HCl-dioxane/HOSO₂NH₂/DMSO. (m) BSA/pH ~9 buffer/22 °C/16 h/dialysis and freeze drying.

DMSO- d_6/D_2O 98:2¹¹; 4.28 for 2, 4.32 for 3, and 4.32 for 11, all in D_2O). Such deshielding has been observed^{13,14} for ring protons that are in van der Waals contact (≤ 2.7 Å) with a hydroxyl, carbonyl, or ether oxygen atom. According to MM2 calculations, it is only the boatlike conformations of GM₃ lactone and lactam that place H-4" in van der Waals contact with the carbonyl oxygen atom. (ii) In the chairlike conformation (Dreiding models), H-3"eq and H-3' are closely situated (~ 2.2 Å); however, no strong NOE effect was observed, thus supporting the boatlike conformation (a ROESY experiment suggested a H-3"eq/H-3' distance of 3.7-4.2 Å). (iii) A molecular mechanics [MM2-(91)^{15,16}] calculation, where both a chair and a boat were used as starting conformations, resulted in boatlike conformations in both cases, with lactones as well as lactams (H-3"eq/H-3' distance ~ 4 Å).

Superimposition and RMS fitting¹⁶ of the low-energy boat conformations of the methyl glycosides corresponding to 2 and 3 (using all ring atoms) showed them to have very similar overall shapes (RMS = 0.097 Å), as depicted in Figure 1.

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Highly Enantioselective Protonation Catalyzed by an Antibody¹

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One of the goals of antibody catalysis² is to facilitate unique chemical transformations. Herein we report an antibody which catalyzes the carbon protonation of a prochiral enol ether. This catalytic system allows highly enantioselective proton delivery, thereby accomplishing a reaction which to date has remained difficult for conventional organic chemistry.

The enantioface selective protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds. Examples have been reported where stoichiometric protonation of a metal enolate by a chiral proton source at low temperature leads to optical yields from 20 to 85% ee.³ Enantioselectivities between 41 and 96% ee for enol protonation were reported for the yeast esterase catalyzed hydrolysis of 1-acetoxycycloalkenes.⁴ Recently, an antibody from our laboratories was shown to catalyze a similar transformation with 42% ee.⁵ All of these reactions involved enolates under basic conditions. The acid-promoted hydrolysis of enol ethers is an interesting alternative which has not been investigated for enantioselectivity.⁶ Hydrolysis of enol ethers

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